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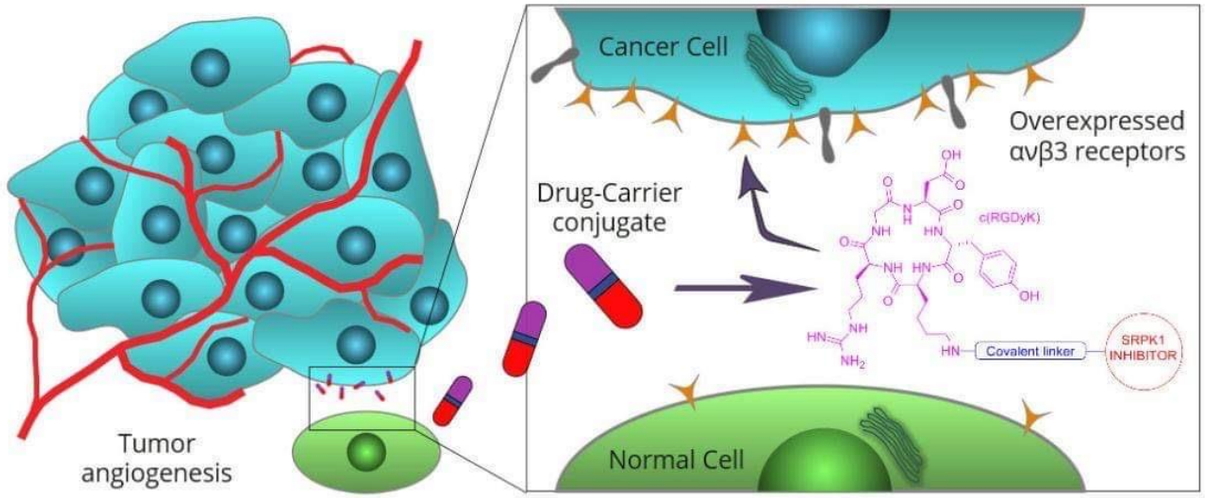
Hellenic Foundation for Research & Innovation

Description of the funded research project

1st Call for H.F.R.I. Research Projects to Support Faculty Members & Researchers and Procure High-Value Research Equipment

Title of the research project: **Synthesis and Biological Evaluation of RGD-Conjugated SRPK1 Kinase Inhibitors for Integrin-Targeted Cancer Therapy**



Principal Investigator: **Vasiliki Sarli**

Reader-friendly title: **Targeted delivery of SRPK1 Kinase Inhibitors in anticancer therapy**

Scientific Area: **Natural Sciences**

Institution and Country: **Aristotle University of Thessaloniki, Greece**

Host Institution: **Aristotle University of Thessaloniki**

Budget: **185460 Euros**
Duration: **36 months**

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Research Project Synopsis

Targeted drug deliver and release represents an attractive approach in the field of cancer treatment. Today, substantial advances have been made to achieve the most of a drug's therapeutic potential and minimize undesirable side effects by conjugation of a drug to specific carriers. The carriers may be peptides, steroids, antibodies or other small molecules that recognize upregulated receptors of cancer cells. The use of peptides has been widely employed and is very appealing owing to their relative ease of synthesis, low toxicity, and high selectivity. Among various types of targeting peptides, Arg-Gly-Asp amino acid sequences are well studied and display high affinity for integrin $\alpha_v\beta_3$ and $\alpha_v\beta_5$ receptors. It is important to note that $\alpha_v\beta_3$ receptors are highly expressed in various types of cancer and are involved in pathological processes such as tumor invasion and metastasis. The main goal of this research project is the development of RGD-conjugated SRPK1 kinase inhibitors for targeted cancer therapy in order to reduce undesired toxicity and improve their efficacy. SRPK1 is a protein kinase that specifically phosphorylates proteins containing serine-arginine-rich (SR) domains. Currently, SRPK1 inhibitors are being investigated as potential anticancer agents and therapeutics in angiogenic-related diseases. The main objectives of the project are: a) synthesis of cancer-targeted peptide conjugates carrying a SRPK1 inhibitor through covalent linkers, b) characterization of the cancer-targeted peptide conjugates and study of their stability in different pH values and/or in blood serum, and c) biological evaluation of the new cancer-targeted peptide conjugates.

Project originality

Analysis of tumor samples demonstrated SRPK1 to correlate with tumor grade and prognosis, with high levels being linked to shorter overall survival than in patients with low-level expression. Emerging evidence support the role of SRPK1 in the pathogenesis of several cancers including breast, colon, pancreas, prostate, glioma and lung cancer. Early studies concerning the potential benefits of SRPK1 inhibition in anticancer therapy are encouraging and efforts have been focused in the development of small molecules that specifically and potently target SRPK1. The novelty of the proposed project is associated with the modification of existing SRPK1 inhibitors with a cancer targeting moiety, aiming at improving their tumor uptake and accumulation, in order to reduce any undesired systemic toxicity and improve their therapeutic effects.

Expected results & Research Project Impact

Cancer remains one of the deadliest diseases affecting mankind. Although, drug discovery and bioscience have seen an enormous progress in the last decades, this was not accompanied by a proportional increase of marketed anticancer drugs. SRPK1 plays a vital role in cancer development and progression, consequently SRPK1 inhibitors are under investigation for the treatment of prostate cancer, acute myeloid leukemia and neovascular eye disease. This proposal is moving in the same direction attempting to develop strategies and technologies for maximizing the efficacy and specificity of currently available SRPK1 inhibitors with the long-term goal to increase the survival and improve the quality of life of cancer patients.

The importance of this funding

H.F.R.I. funding offers me the unique opportunity to conduct high quality and innovative research at Aristotle University of Thessaloniki (AUTH). It is a demanding and multidisciplinary program between Chemists, Biochemists and Biologists. The current project will finance two young PhD students in my research group to broaden their scientific horizons and acquire new skills that will help them develop further their career in the field of medicinal chemistry as independent researchers.

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COMMUNICATION

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